REMARKS

This amendment is submitted in an earnest effort to bring this case to issue without delay.

Applicants wish to reiterate their claim to the benefit of their Hungarian Patent Application P0300929 filed 9 April 2003 pursuant to the International Convention. A certified copy of the Hungarian Patent Application has already been made of record in PCT/HU2004/000032 filed 7 April 2004 of which the instant application is the US National Phase. The Examiner has already acknowledged Applicants' perfected right of priority.

Applicants have canceled original claims 1 through 5 and are submitting new claims 6 through 17. Antecedent basis for the new claims may be found in the specification on pages 3 through 12. Thus claims 6 through 17 are now in the application and are presented for examination.

The Examiner has rejected method of treatment claim 5, last presented, under 35 USC 112, first paragraph, for claiming the invention too broadly beyond the scope of the enabling disclosure as well as all claims under 35 USC 103 as obvious in view of the cited prior art. Applicants are now submitting new claims 6 through 17 to replace the original claims 1 through 5. The reason why the Examiner has rejected the original claim 5 under 35 USC 112, first paragraph, is the language in the preamble "preventing spasticity and/or pain" which the Examiner considers to be beyond

the scope of the enabling disclosure since the active ingredients are believed to relieve or inhibit spasticity and/or pain, but not to prevent it, which implies that the pain and/or spasticity have been completely eliminated. In the new method of treatment claims 10, 11, 16 and 17 now presented, Applicants have used the word "inhibiting" instead of "preventing". Thus no rejection of any claim now presented should be maintained under 35 USC 112, first paragraph, on the grounds of lack of an enabling disclosure.

The Examiner has rejected original claims 1 through 5 as obvious under 35 USC 103 based upon US Patent 4,906,638 to PONTECORVO et al in combination with JAPAN 53040779 (abstract). The Examiner argues that PONTECORVO discloses pharmaceutical compositions for treating epilepsy and other convulsions where the compositions contain both dextromethorphan and compounds with established pharmaceutical utility in the treatment of epilepsy and other convulsive disorders. The Examiner argues that the dextromethorphan potentiates the anti-convulsive effect of the compounds with established pharmaceutical utility in the treatment of epilepsy and other convulsive disorders. The Examiner admits that there is no disclosure in the reference of tolperisone or eperisone as the compounds used to treat epilepsy or other convulsive disorders. However, the Examiner then cites JAPAN 53040779 for its disclosure that tolperisone has central nervous system relaxant, anti-convulsive, and anti-asthmatic properties. The Examiner concludes that it would be obvious to those "skilled

in the art" to employ tolperisone in place of the anti-convulsive compounds disclosed in PONTECORVO et al with the expectation that the dextromethorphan combined with tolperisone would lead to a highly effective anti-spasmodic pharmaceutical composition.

Applicants first of all wish to draw a distinction between treating pain and treating spasticity and so have submitted separate claims to compositions and methods of treatment with each utility. Claims 6 through 11 are directed to the compositions and methods of treatment for inhibiting pain. Applicants point to page 1, fourth paragraph, of the present application where it is disclosed in the background portion of this application that tolperisone per se is not a recognized analgesic agent, indicating that the compound per se has little or no ability to inhibit pain. On page 2, second full paragraph of the present application, it is further disclosed in the background discussion of the prior art that dextromethorphan has no per se activity to inhibit pain. In view of the above, Applicants believe that the data on page 10 of the present application showing the high efficacy of the claimed compositions for inhibiting pain is unexpected, and that there is no indication or suggestion in either PONTECORVO et al or JAPAN 53040779 that either tolperisone or eperisone would inhibit pain or that dextromethorphan would per se inhibit pain or would potentiate the analgesic effects of tolperisone or eperisone. Thus the compositions and methods of claims 6 through 11 are both novel and unobvious. The data in Table 6 of the present application show

that tolperisone has only a slight per se analgesic effect and dextromethorphan per se has no analgesic effect, but that the combination of both ingredients shows a surprisingly strong analgesic effect. Thus dextromethorphan potentiates the analgesic effect of tolperisone or its homolog eperisone.

Applicants also note that tolperisone and eperisone fitting within the scope of present Formula (I) are structurally far removed from either Carbamazepine or CPP, the two anticonvulsive compounds disclosed in PONTECORVO et al exhibiting co-action with dextromethorphan. Carbamazepine is a benzo(b,f)azepine, a tricyclic compound with an azepine ring in the center. The compound CPP is 3-(2-carboxypiperazine-4-yl)propyl-1-phosphono acid and is therefore a phosphorus-containing compound. The present Formula (I) compounds contain no azepine ring and no phosphorus atom. Thus it does not follow from PONTECORVO et al even combined with JAPAN 53040779 that there would be any kind of co-action between tolperisone or eperisone and dextromethorphan, either as an analgesic or as an anti-spasmodic. In addition, there is no disclosure in JAPAN 53040779 that tolperisone and eperisone are anti-convulsive compounds; the reference discloses that these compounds are central muscle relaxants, antitussives, and anti-asthma compounds, and thus the combination of these two references is improper. Therefore Carbamazepine and CPP are completely different, from tolperisone and eperisone, both in terms of structure and in terms of pharmaceutical utility, thereby providing

further reasons why one skilled in the art would not expect substitution of the anticonvulsives of PONTECORVO et al with tolperisone or eperisone would result in combination with dextromethorphan in a composition with strong analgesic activity. In view of the above Applicants believe that claims 6 through 11 are directed to unobvious subject matter and that no rejection of these claims should be maintained under 35 USC 103 as obvious in view of the cited combination of references.

Applicants now turn to new claims 12 through 17. These claims are directed to synergistic pharmaceutical compositions for treating spasticity as well as to a method of treating spasticity using the synergistic compositions. These claims require a weight ratio of 40 to 60 parts of tolperisone or eperisone and 10 parts of dextromethorphan. These compositions with this particular weight ratio are indeed synergistic. Applicants note that the data in Table 3 on page 6 of the application show a synergistic anti-spasmodic effect between tolperisone and dextromethorphan in a proportion of 40 to 60 parts tolperisone to 10 parts dextromethorphan. Note that 10 mg/kg ip of dextromethorphan are 8% effective in inhibiting tremor and 40 mg/kg ip of tolperisone per se is 27% effective in inhibiting tremor, but a combination of the two ingredients in those proportions is 59% effective. Merely adding up the two percentages would mean that one would expect only a 35% effective inhibition. Thus these two ingredients in this proportion would be synergistic under the additivity test. See In

re Kollman and Irwin, 201 USPQ 193 (CCPA 1979). The same analysis applies to 10 mg/kg ip of dextromethorphan and 60 mg/kg ip of tolperisone. Based on these data, Applicants are submitting new claims 12 through 17.

There is no suggestion in the prior art that the compositions and method of treatment in new claims 12 through 17 would result in a synergistic pharmaceutical composition for treating spasticity as opposed to merely exhibiting the additive effects of the combination of the two active ingredients. PONTECORVO et al discloses only that dextromethorphan potentiates the anticonvulsive effects of compounds that are different from tolperisone or eperisone, in terms of both structure and activity, as explained hereinabove, and JAPAN 53040779 discloses only that tolperisone or eperisone have per se central muscle relaxant, anti-tussive and anti-asthma activity. Thus no rejection of claims 12 through 17 now presented should be maintained as obvious under 35 USC 103 in view of the cited prior art.

Applicants believe that all claims now presented are in condition for allowance and a response to that effect is earnestly solicited.

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